REMARKS

Telephone interview

Applicants' representative wishes to thank Examiner Rawlings for extending the courtesy of a telephone interview on October 18, 2001, and for the helpful discussion that ensued. Applicants believe that the remarks herein are fully responsive to the questions that were raised by the Examiner.

Status of the claims

Claims 1-5, 20-24, 26-37, 39-40, 42,-43, 54-56, 59-65 and 67-73 are under examination in the present application. By virtue of this response, claims 26 and 33 have been amended and new claims 74-97 have been added. Accordingly, claims 1-5, 20-24, 26-37, 39-40, 42-43, 54-56, 59-65, and 67-97 are currently under consideration. For the Examiner's convenience, and as requested by the Examiner, a set of currently pending claims after entry of amendment is attached as Appendix A.

The claim amendments and new claims are supported by the specification as follows:

Support for the amendment to claim 26 may be found for example on page 66, line 26 - page 67, line 6. Support for the amendment to claim 33 may be found for example on page 72, lines 21-25. Support for new claim 74 may be found for example on page 40, lines 13-20. Support for new claim 77 may be found for example on page 64, lines 14-16, page 64, line 19 - page 65, line 1, and page 65, lines 4-8. Support for new claim 78 may be found for example on page 72, lines 21-25. Support for new claim 79 may be found for example on page 72, lines 13-18. Support for new claim 80 may be found for example on page 71, lines 1-3 and 15-16. Support for new claims 81, 85, 89, and 93 may be found for example on page 89, line 24 - page 90, line 12. Support for new claims 75, 82, 86, 90, and 94 may be found for example on page 90, lines 18-25. Support for new claims 76, 83, 87, 91, and 95 may be found for example on page 94, lines 10-15. Support for new claim 84 may be found for example on page 71, lines 1-3 and

15-19. Support for new claims 88 and 92 may be found for example on page 64, lines 21-23, page 71, lines 1-27, and in Figures 1, 2, and 3. Support for new claim 96 may be found for example on page 40, lines 13-20 and in Figures 1, 2, and 3. Support for new claim 97 may be found for example on page 64, lines 21-23 and in Figure 3.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**."

With respect to any claim amendments or cancellations, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Applicants have carefully considered the points raised in the Office Action and believe that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance.

Request for rejoinder

Applicants reiterate their request for rejoinder of presently excluded method claims, to the extent that they incorporate all the limitations of the product claims. The Office has indicated that once allowable product claims are identified, then method claims which incorporate all the limitations of the product claims and which do not present any new issues may be rejoined (paper no. 19, page 2).

Rejection under 35 U.S.C § 112, second paragraph

Claim 26 stands rejected under 35 U.S.C as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Office Action states that claim 26 was rejected in the previous Office Action (paper 25) for

reciting "tandem repeat sequences," allegedly without further disclosing what tandem sequences within SEQ ID NO:33 are being claimed.

Applicants note that claim 26 was previously amended, in the response to paper 25, to recite "wherein said tandem repeat sequence is contained in SEQ ID NO:33." In that response, Applicants noted that the specification amply describes the term "tandem repeat sequence" (see for example, p. 66, lines 19-21, Figure 23, and SEQ ID NO:33), and that one of skill in the art would understand what is meant by this phrase. However, in the interest of expediting prosecution, claim 26 was amended to recite "wherein said tandem repeat sequence is contained in SEQ ID NO:33." The Office Action states that despite the amendment, recitation of the term "tandem repeat sequence" still renders claim 26 unclear. Applicants maintain that claim 26, as currently pending, is clear, in view of the recitation in the claim that the tandem repeat sequence is contained in SEQ ID NO:33. As noted above, this term is described in the specification. The "20 amino acid tandem repeat within HMFG" (p. 66, lines 19-21 of the specification) is represented in the specification as the 20 amino acid sequence of SEQ ID NO:33. This sequence is also represented in Fig. 23, where its sequence alignment with 11D10 CDRs is shown. However, in the interest of expediting prosecution, Applicants have removed the term "tandem repeat" from the claim. The claim now recites "[t]he polypeptide of claim 20, wherein the polypeptide contains a sequence of at least 2 contiguous amino acids which are identical in forward or reverse orientation to 2 contiguous amino acids of a sequence in human mucin from human milk fat globule (HMFG), wherein said HMFG sequence is contained in SEQ ID NO:33."

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

Rejection under 35 U.S.C § 102(b)

Applicants acknowledge with appreciation the withdrawal of the 35 U.S.C. § 102(b) rejection with respect to Chakraborty et al. (*Cancer Research*, Vol. 55, pp. 1525-1530, 1995).

Claims 1-5, 20-27, 31-33, 36-37, 39-40, 42-43, 54-56, 59-65 an 67-73 stand rejected under 35 U.S.C § 102(b) as allegedly anticipated by either Chatterjee (*Antigen and Antibody*, 1994), Chatterjee et al. (*Cancer Immunol.*, 1994), Chakraborty et al. (*Proc. Am. Assoc. Cancer*, 1994), or Chakraborty et al. (*Immunotherapy*, 1995). Applicants respectfully traverse this rejection.

As discussed during the telephone interview of October 18, 2001, Applicants note that they have addressed the rejection based on these references on two previous occasions of record, both in a Preliminary Amendment filed on October 8, 1998 and in the Amendment filed on March 26, 2001 in response to the last Office Action. Further, Applicants submitted declarations on September 30, 1999, signed by M. Chatterjee, K. Foon, and S. Chatterjee, which discuss the lack of public availability of 11D10 prior to the December 20, 1995 priority date of the instant application (and prior to the January 29, 1996 filing date of priority application U.S. Serial No. 08/591,965), as well as the role/contribution of the authors of the cited references.

Applicants maintain that the cited references are not appropriate § 102(b) references. As discussed previously in the Preliminary Amendment filed on October 8, 1998 and in the Amendment filed on March 26, 2001 in response to the second Office Action, none of the cited publications anticipates the pending claims because (a) the cited references are not enabling because they do not teach and/or enable obtaining the 11D10 antibody, and do not disclose the amino acid sequence or polynucleotide coding sequence for the variable regions of 11D10, and thus cannot be used as prior art references; and (b) neither the 11D10 antibody nor the hybridoma producing 11D10 were made available to the public. Applicants previously discussed in detail the mechanism of antibody formation, as well as the uniqueness of the 11D10 sequences, which were not disclosed in any of the cited references, in the Preliminary Amendment filed on October 8, 1998. A summary of this discussion is presented below. As requested by the Examiner, a copy of the Preliminary Amendment, containing the previous discussion of this issue in its entirety, is attached as Appendix B.

response to the same antigen may have substantially different variable region sequences. Therefore, the chances of producing an antibody with the identical sequence to 11D10, by immunizing a mouse with an antibody specific for binding of HMFG and producing a hybridoma, is vanishingly low.

An extensive comparison of the sequence of 11D10 with published sequences found in GenBank was presented in the Preliminary Amendment filed on October, 8, 1998 and in a declaration by Dr. Sunil Chatterjee, submitted on September 30, 1999, which is attached to this response for the Examiner's convenience as Appendix C. This declaration presents a comparison with other antibody sequences in GenBank and shows that 11D10 heavy and light chain variable regions are extensively mutated by comparison to other antibody variable regions. Appendix B of the Preliminary Amendment, which is also attached to this response for the Examiner's convenience as Appendix D, included a calculation of the number of possible antibody molecules that are as extensively mutated as 11D10 and capable of binding the same antigen. *The results of the calculation indicated that even with conservative assumptions, the occurrence of a cell producing an entire 11D10 variable region is on the order of* 5.4×10^{35}. Gene selection, splicing, and somatic mutation all contribute to this number. *It has also been calculated that since so few specific cells can be fused, identified, and expanded from each immunized mouse, it would take at least about* 5×10^{28} *mice to produce an antibody as rare as 11D10.*

In summary, in view of the extensive mutation in 11D10, it is in all practical terms impossible for anyone to obtain an antibody molecule with identical variable region sequences to 11D10 simply by immunizing another animal, even using the exact protocol used to obtain 11D10 that is taught in the cited references.

(b) Neither the 11D10 antibody nor the hybridoma producing 11D10 was made available to the public.

Neither the 11D10 antibody nor the hybridoma producing 11D10 were made accessible to the public before filing the priority application.

For the Examiner's convenience, attached to this response as Appendix E are copies of previously-submitted declarations by the inventors in which they state that the 11D10-producing cell lines and the antibody produced by these cells remained under their strict and exclusive control prior to the December 20, 1995 priority date for this application (as well as prior to the January 29, 1996 filing date of priority application U.S. Serial No. 08/591,965), and that neither the cell lines nor the antibodies were made available to the public prior to these priority dates.

Summary

Because of the uniqueness of the 11D10 antibody and the virtual impossibility of regenerating it in a second animal, the invention can only be practiced by either: (a) obtaining the antibody (or a polynucleotide encoding it) from the 11D10-producing hybridoma cell line; or (b) synthetically producing an antibody with identical amino acid sequences, based on the 11D10 sequence data. The invention cannot be said to be in possession of the public at the time of filing of the priority application(s). Therefore, the cited references do not provide sufficient disclosure for one skilled in the art to reproduce 11D10 and do not anticipate the invention. Merely referring to the antibody by name only ("11D10") in the references does not enable practicing the invention as claimed.

Applicants note that this issue has been addressed in other cases by the same inventors that have been allowed and have issued as U.S. patents. See U.S. Patent Nos. 5,977,315 (relating to anti-idiotypic antibody 3H1), and 5,977,316 and 5,612,030 (relating to anti-idiotypic antibody 1A7).

In view of the foregoing, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 102(b).

Rejection under 35 U.S.C. § 103(a)

Claims 1-5, 20-27, 31-33, 36-37, 39-40, 42-43, 54-56, 59-65, 67-68 stand rejected under 35 U.S. C § 103(a) as allegedly unpatentable over Chatterjee et al. (*Antigen and Antibody Molecular Engineering*, cited *supra*), in view of Adair et al. (WO 91/09967). Applicants respectfully traverse this rejection.

The Office Action states that it would have been obvious to combine the teachings of Chatterjee et al., which allegedly discloses a method of making the 11D10 antibody and Adair, which allegedly discloses a method of making a humanized antibody, to arrive at the instant invention. The Office Action states that one would have been motivated because Chatterjee et al. allegedly teach that the 11D10 antibody is an antibody that binds to the HMFG found on breast cancer cells and contains CDRs specific for HMFG.

As a preliminary matter, Applicants note that the Office Action reflects a misunderstanding with respect to the technology involved in the instant invention. Antibody 11D10 is an anti-idiotypic antibody, and as such does not bind to HMFG, but rather contains at least one region that putatively resembles at least one region of HMFG. Therefore, 11D10 does not contain CDRs specific for HMFG. Rather, one or more CDRs may conformationally or structurally (linearly) mimic an antigenic epitope of HMFG, rendering 11D10 capable of stimulating a specific immune response against HMFG.

Further, Applicants note that not all of the claims rejected under § 103(a) are directed toward a polynucleotide comprising the CDR regions of 11D10, a fusion polypeptide thereof, or a humanized antibody thereof, as the Office Action states. Claims 1-5 are directed to monoclonal anti-idiotypic antibody 11D10 produced by hybridoma cell line ATCC No. HB 12020 or progeny thereof. Claim 37 is directed to a composition comprising anti-idiotype antibody 11D10 and a pharmaceutically acceptable excipient. Claims 40 and 43 are directed to an immunogenic composition comprising anti-idiotypic antibody 11D10 and a pharmaceutically acceptable excipient. Claims 54 and 55 are directed to a kit comprising anti-idiotypic antibody 11D10 in suitable packaging. Claims 59 and 60 are directed to a composition comprising an

immunologically effective amount of anti-idiotypic antibody 11D10. Therefore, inclusion of these claims in the § 103(a) rejection is improper.

With respect to the statement that it would have been obvious for one of ordinary skill in the art to combine the teachings of Chatterjee and Adair to derive the instant invention with a "reasonable expectation of success," Applicants respectfully note, as discussed above, that Chatterjee et al. did not disclose either the polynucleotide or the amino acid sequence of antibody 11D10. It would have been virtually impossible for one of skill in the art to derive antibody 11D10 through the teachings of Chatterjee et al. Without the sequence of the polypeptide, one of skill in the art could possibly produce a different anti-idiotypic antibody using the methods of Chatterjee et al, but could not produce 11D10, which is a unique protein. Without the sequences required for production of 11D10, the teachings of Adair would not be sufficient for one of skill in the art to produce a polypeptide containing CDRs of 3H1, a humanized antibody based on CDRs of 3H1, or a fusion protein based on these sequences. Therefore, one of skill in the art would not have a "reasonable expectation of success" in deriving the claimed invention by combining the two cited references. Also, as discussed above, neither 11D10 nor the hybridoma producing 11D10 were made publicly available prior to filing of the priority application.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

Withdrawal of all previous rejections

The Examiner states that all other rejections cited in the previous Office Action are withdrawn. Applicants acknowledge with appreciation the withdrawal of all other previous rejections, such as the rejections under 35 U.S.C. §§ 112, first paragraph, and 102(f), to the extent that they have not been reiterated in this Office Action. Applicants would appreciate the Office officially withdrawing these rejections.

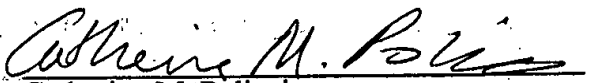
CONCLUSION

Applicants have, by way of the amendments and remarks presented herein, removed the issues for the rejections and addressed all issues that were raised in the outstanding Office Action. Accordingly, reconsideration and allowance of the pending claims are respectfully requested. If it is determined that a telephone conversation would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the unlikely event that the fee transmittal is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 304142000321. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: November 7, 2001

By: 

Catherine M. Polizzi
Registration No. 40,130

Morrison & Foerster LLP
755 Page Mill Road
Palo Alto, California 94304-1018
Telephone: (650) 813-5651
Facsimile: (650) 494-0792

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

26. (Thrice Amended) The polypeptide of claim 20, wherein the polypeptide contains a sequence of at least 2 contiguous amino acids which are identical in forward or reverse orientation to 2 contiguous amino acids of a [tandem repeat] sequence in human mucin from human milk fat globule (HMFG), wherein said [tandem repeat] HMFG sequence is contained in SEQ ID NO:33.

33. (Twice Amended) The fusion polypeptide of claim 27, comprising the light chain variable region and the heavy chain variable region of antibody 11D10, wherein the light chain variable region and the heavy chain variable region are contained in SEQ ID NO:2 and SEQ ID NO:4, respectively.